# The evolving evidence base for coronary artery bypass grafting and arterial grafting in 2021: How to improve vein graft patency

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Coronary artery bypass grafting (CABG) is foundational to managing multivessel coronary artery disease. The internal thoracic artery (ITA) remains the gold standard for left anterior descending artery (LAD) grafting. Although saphenous vein grafts (SVGs) may be considered for non-LAD targets, the right ITA (RITA) and radial artery (RA) are associated with improved outcomes[1] and thus are more commonly used for CABG. A recent systematic review and a network meta-analysis of 150,000 patients[2,3] highlighted that the use of RA was associated with a lower risk of major adverse cardiovascular events (MACE) at 5 and 10 years and with a higher rate of patency at 5 years. Moreover, the growing interest in and evidence supporting multiple arterial grafting has resulted in their overall favorable consideration in professional society guidelines for myocardial revascularization,[4] even though most of the published evidence supporting the RITA is observational. Conversely, up to 20% of SVGs reportedly fail within 1 year post-CABG, owing primarily to technical errors, thrombosis, and intimal hyperplasia, and an additional 20% to 25% fail by 10 years post-CABG owing to arteriosclerosis.[5] The Project of Ex-Vivo Vein Graft Engineering via Transfection (PREVENT) IV, the largest angiographic trial to date (n = 3014 across 107 sites), found angiographic SVG occlusion in >26% of grafts overall and at least 1 SVG occlusion in 42% of patients at 12 to 18 months post-CABG.[6] A recent meta-analysis of early SVG occlusion suggests that approximately 11% of grafts occlude within 1 year post-CABG.[7]

Despite the evidence supporting use of the RITA and RA, the potential of SVGs cannot be dismissed, given that
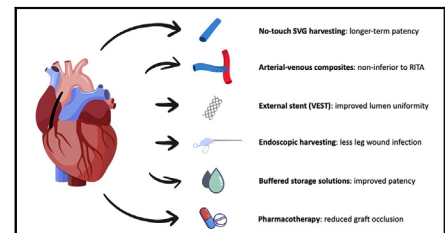
Improving saphenous vein graft patency for coronary artery bypass grafting.

CENTRAL MESSAGE

Saphenous vein grafts remain the most common conduits for coronary artery bypass grafting despite limited durability. Various techniques have arisen to improve vein graft patency and outcomes.

See Commentaries on pages 110 and 112.

>80% of CABG conduits in the United States currently comprise SVGs.[4] In addition, there are specific contraindications to using the RITA or RA. Accordingly, methods to improve vein graft patency are warranted. In this Invited Expert Opinion, we describe the no-touch saphenous vein graft (NT-SVG), ITA anastomosed SVG composites, externally supported SVGs (VEST), endoscopically harvested SVGs, SVG storage solutions, and pharmacotherapy as promising techniques to improve vein graft patency (Figure 1).

NT-SVG HARVESTING

NT-SVG is a variation of SVG whereby harvesting of the vein graft occurs with a small amount of surrounding tissue. The pedicled graft is harvested atraumatically and without manual dilatation and is checked for leaks when subjected to aortic pressure. Souza[8] was the first to report a case series on NT-SVG in 1996. Since then, an increasing number of reports have shown improved patency compared with conventional SVG (C-SVG) as well as patency approaching that achieved with the left ITA (LITA) over the long term.
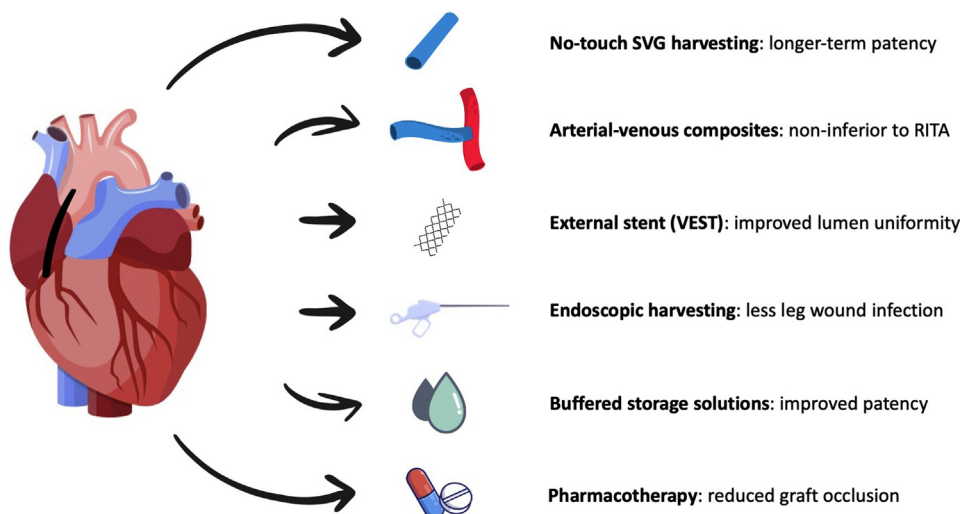
FIGURE 1. Comparison of techniques to improve saphenous vein graft (SVG) patency for coronary artery bypass grafting. *RITA*, Right internal thoracic artery; *VEST*, externally supported SVG.

Recent reports even suggest that NT-SVG is associated with improved health-related quality of life after CABG.[9] However, large studies showing improved clinical outcomes are lacking, and the effects on health-related quality of life need to be confirmed in a standardized manner in future studies.

The growing evidence supporting NT-SVG has led to favorable considerations in recent societal guidelines. The 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines on Myocardial Revascularization recommend NT-SVG as a class IIa, level of evidence (LoE) B recommendation when an open harvesting technique is used.[10] These recommendations were based on the work of Samano and colleagues,[11] who showed 16-year patency with NT-SVG, and Dreifaldt and colleagues,[12] who found a similar 8-year patency for NT-SVG compared with RA grafts. The 2011 American College of Cardiology Foundation/American Heart Association (AHA) Guideline for CABG Surgery did not specify any SVG technique in its recommendations.[13]

To date, 4 randomized controlled trials (RCTs) have compared the performance of NT-SVG harvesting compared with C-SVG harvesting, 3 of which reported patency results (Table 1). At a mean follow-up of 18 months, Souza and colleagues[15] reported a higher rate of leg wound complications with NT-SVG compared with C-SVG (11.1% vs 4.3%; n = 156).[15] The group later reported patency rates in the 2 groups of patients of 90% versus 76% (P = .01) at a mean follow-up of 8.5 years[16] and 83% versus 64% (P = .03) at a mean follow-up of 16 years,[11] with NT-SVG patency rates not statistically worse than those of LITA grafts.[11,16] SUPERIOR SVG[18] (n = 250) was the first multicenter angiographic trial comparing NT-SVG and C-SVG. The trial's primary outcome, SVG occlusion or cardiovascular mortality at

1 year, was not statistically different between the groups (5.5% for NT-SVG vs 10.6% for C-SVG; P = .15), and neither was SVG stenosis or total occlusion (7.8% for NT-SVG vs 15.0% for C-SVG; P = .11). However, the NT-SVG group had a significantly greater incidence of early vein harvest site infection at 1 month (23.3% vs 9.5% for C-SVG; P < .01). Leg assessment scores (Total Leg Scores) were significantly worse in the NT-SVG group at 1 month (adjusted difference, 2.58; P < .001) and 3 months (adjusted difference, 2.30; P = .002) but were comparable in the 2 groups at 1 year (adjusted difference, 1.12; P = .407). Finally, Pettersen and colleagues randomized 100 patients in the IMPROVE-CABG trial to pedicled versus conventional harvesting to assess 5-year angiographic SVG function.[19] Early perioperative findings have been promising, suggesting comparable postoperative bleeding and leg wound infection rates, and long-term findings are expected in the near future.

Meta-analytic findings,[18] including SUPERIOR SVG, concluded that graft occlusion was significantly reduced with NT-SVG versus C-SVG as treated (odds ratio [OR], 0.49; 95% confidence interval [CI], 0.29-0.82; P = .007) at 1 year across 3 trials and 1 observational study. A recent network meta-analysis of patency confirmed significantly reduced graft occlusion in NT-SVG compared with C-SVG.[27] Although a majority of the early NT-SVG experience and reports stem from the same center, 2 major ongoing RCTs will add further to our knowledge of NT-SVG. In Sweden and Denmark, SWEDEGRAFT[20] has recruited 902 patients to assess graft failure by computed tomography angiography, repeat target vessel revascularization, or death at 2 years as the primary composite endpoints and leg wound assessment scores as secondary endpoints (ClinicalTrials.gov identifier

TABLE 1. Randomized controlled trials evaluating select saphenous vein graft harvesting techniques to improve graft patency

Study	Year of primary trial completion	Sample size	Follow-up	Intervention(s)	Primary outcomes	Secondary outcomes
No-touch SVG						
Dreifaldt et al[14] Dreifaldt et al[12]	2014	108	36 mo (mean) 97 mo (mean)	No-touch SVG vs radial artery graft	SVG patency by angiography at follow-up	Incidence of perioperative and postoperative myocardial infarction, death, or need for revascularization
Souza et al[15] Souza et al[16] Samano et al[11]	2011	156	18 mo (mean) 8.5 y (mean) 16 y (mean)	No-touch SVG vs standard open vs intermediate technique	SVG patency by angiography at follow-up	Stenosis in grafts at follow-up
PATENT-SVG[17]	2012	17	12 mo	No-touch SVG vs standard open harvesting	SVG morphometry and early markers of vascular smooth muscle cell activation	Leg wound healing and functional recovery at 3 and 12 mo
SUPERIOR-SVG[18]	2015	250	12 mo	No-touch SVG vs standard open harvesting	Incidence of complete SVG occlusion at 1 y or death due to cardiovascular or unknown causes	• Significant stenosis and MACCE at 1 y • Leg adverse events and leg quality of life at 1 y
IMPROVE-CABG[19]	2016	100	5 y	Pedical vs conventional SVG harvesting	SVG function by angiography at 6 mo and 5 y	• Morphological appearance of SVG at 6 mo and 5 y • Leg wound complications at 6 wk • Postoperative complications at discharge, 6 wk, 6 mo, and 5 y
SWEDEGRAFT[20]	Ongoing	902	2 y	No-touch SVG vs standard open harvesting	• SVG occlusion or stenosis on CCTA at 2 y or earlier • Death within 2 y	• Wound healing in SVG sites at 2 y • Incidence of MACE at 2 y
Wang et al[21]	Ongoing	2655	12 mo	No-touch SVG vs standard open harvesting	SVG occlusion on CCTA at 3 mo	• MACCE at 3 and 12 mo • SVG occlusion at 1 y
ITA anastomosed SVG composite						
SAVE-RITA[22]	2012	224	5 y	SVG vs RITA as Y-composite graft	SVG or RITA patency by angiography at 1 y	• Overall survival at 1 and 4 y • Incidence of MACCE at 1 and 4 y
Externally supported SVGs (VEST)						
VEST I[23]	2013	30	12 mo	VEST-supported vein graft	• SVG intimal hyperplasia area by intravascular ultrasound at 1 y • Incidence of MACCE at 6 wk	SVG failure, ectasia, and Fitzgibbon classification at 1 y

(Continued)

TABLE 1. Continued

Study	Year of primary trial completion	Sample size	Follow-up	Intervention(s)	Primary outcomes	Secondary outcomes
VEST III[24]	2019	184	2 y	VEST-supported vein graft	• Proportion of SVGs with perfect patency at 2 y	• Intimal hyperplasia area at 2 y • MACCE at 2 y • SVG failure at 2 y • Early SVG failure at 6 mo
VEST IV[25]	2013	30	4.5 y (mean)	VEST-supported vein graft	• MACCE at follow-up • Intimal hyperplasia and thickness at follow-up • Graft occlusion and Fitzgibbon perfect patency rates at follow-up	Not specified
VEST Pivotal	Ongoing	224	5 y	VEST-supported vein graft	Intimal hyperplasia area and graft occlusion at 1 y	• Lumen diameter uniformity at 1 y • Vein graft failure (≥50% stenosis) by cardiac angiography at 1 y • Incidence of MACCE annually over 5 y
SVG storage solutions Perrault et al[26]	2016	125	12 mo	DuraGraft graft storage solution	• Change in wall thickness between 1 and 3 mo • Change in maximum narrowing between 1 and 12 mo	• MDCT angiography measurements for wall thickness, lumen diameter, maximum narrowing, and vessel diameter at 3 and 12 mo • Changes in MDCT angiography measurements between 1 and 3 mo and between 1 and 12 mo • Incidence of SVG thrombosis and occlusion, MACE, angina, arrhythmias, shortness of breath, significant stenosis

SVG, Saphenous vein graft; *MACCE*, major adverse cardiovascular and cerebrovascular events; *CABG*, coronary artery bypass grafting; *CCTA*, coronary computed tomography angiography; *MACE*, major adverse cardiovascular events; *ITA*, internal thoracic artery; *RITA*, right internal thoracic artery; *VEST*, externally supported saphenous vein graft; *MDCT*, multidetector computed tomography.

NCT03501303). In China, Wang and colleagues[21] have recruited 2655 patients in a multicenter RCT with graft occlusion at 3 months as the primary endpoint and a major adverse cardiovascular and cerebrovascular event (MACCE) at 3 and 12 months postoperatively and graft occlusion at 12 months postoperatively as secondary endpoints (ClinicalTrials.gov identifier NCT03126409).

ITA ANASTOMOSED SVG COMPOSITE

An arterial–arterial composite graft is a strategy to achieve more complete arterial revascularization with fewer conduits while also reducing aortic manipulation and decreasing neurologic events. An arterial–venous composite graft is usually considered a bail-out strategy for patients with limited conduit options and/or a hostile aorta. Theoretical advantages of arterial–venous composite are that the SVG is subjected to dampened pressure waves from the ITA compared with the aorta, whereas the SVG may be bathed with vasodilatory, antithrombotic, and antiatherosclerotic mediators from the ITA due to a proximal anastomosis to the LITA. However, a graft size mismatch and the greater sensitivity of arterial grafts to competitive flow compared with SVGs may lead to the steal sign or string sign (ie, diffuse narrowing of part of or the entire graft). This has been observed in up to 7% of RA grafts.[4] In addition, the usual concerns about T-graft (ie, side-to-end) anastomoses remain, including obstruction due to kinking of the graft or misplacement of the pedicle, competition of flow with bypassed vessels, and the need for technical experience.

Current trial evidence evaluating ITA-anastomosed SVG composites remains scarce (Table 1). The SAVE RITA trial (n = 224) found that SVG composites were noninferior to the RITA as Y-composites proximally anastomosed to LITAs graft at 1 year (97.1% for SVG composites vs 97.1% for RITA composite grafts; $P < .001$), albeit with a large (8%) noninferiority margin.[22] In addition, a recent propensity-matched analysis of 196 patients suggested further improvement of 1-year arterial–venous composite patency when using the NT-SVG for the venous limb (97.3% for NT-SVG vs 92.6% for minimal manipulation; $P = .051$).[28] To date, these superb results have been reported only from a single center, however; larger multi-institutional studies are needed to confirm these findings before the widespread adoption of this technique.

VEST

A more recently introduced technique is the use of a cobalt–chromium mesh stent to externally support the SVG and improve graft hemodynamic properties. The VEST device (Vascular Graft Solutions, Tel Aviv, Israel) has been approved for clinical use in Europe following a series of VEST trials (Table 1). VEST I (n = 30) was a first-in-human trial highlighting a reduced mean intimal hyperplasia area (4.37 ± 1.40 mm^2 vs 5.12 ± 1.35 mm^2;

$P = .04$) at 1 year for stented SVGs versus nonstented SVGs.[23] VEST III (n = 184) later confirmed these findings at 2 years with a substantially larger sample.[24] Although patency rates were comparable for stented and nonstented SVGs (78.3% vs 82.2%; $P = .43$), the Fitzgibbon patency scale was improved significantly (OR, 2.02; $P = .03$), and mean intimal hyperplasia area (3.07 ± 0.37 mm^2 vs 3.96 ± 0.38 mm^2; $P < .001$) and thickness (0.26 ± 0.03 mm vs 0.34 ± 0.31 mm; $P < .001$) were reduced. The longer but smaller VEST IV (n = 21) found higher Fitzgibbon perfect patency with VEST at 1 year (81% vs 48%; $P = .002$) and 5 years (79% vs 50%; $P = .002$) compared with C-SVG.[25] Vest II (n = 30) provided a postmarket clinical assessment of the VEST device to the right coronary artery to identify graft failure by CT angiography at 3 to 6 months.[29] Avoidance of external stent fixation to anastomoses and the use of metallic clips to ligate SVG branches was found to improve the patency of stented SVGs to the right coronary territory (86.2%), in agreement with VEST I findings (88.8%).[23]

These findings are encouraging and are being longitudinally assessed in the VEST EU Registry (n > 1000), an ongoing prospective cohort (2017-2025). Although VEST is yet to be approved in North America, the Food and Drug Administration is running the VEST Pivotal RCT (n = 224) (ClinicalTrials.gov identifier NCT03209609) to confirm earlier trial results. The primary study outcome is intimal hyperplasia as assessed by intravascular ultrasound at 12 months.

ENDOSCOPICALLY HARVESTED SVG

To address the leg wound infections, healing issues, and associated postoperative pain observed with NT-SVG, endoscopic harvesting of the SVG has been proposed and successfully adopted. However, the technical complexity of endoscopic SVG harvesting requires a longer learning curve and thus is more commonly performed by experienced surgeons, which compromises residents' ability to adequately learn this technique.[30] A meta-analysis of 267,525 patients found that leg wound infections and complications were significantly reduced and graft occlusion was increased across all studies, although the latter finding was not confirmed by analysis of 2 RCTs alone.[31] This is recognized by the 2018 European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines,[10] which recommend that endoscopic harvesting of SVGs be performed by experienced surgeons to reduce harvest site infection (class IIa, LoE A recommendation). Despite its advantages, a potential risk is CO_2 embolism development during endoscopic SVG harvesting, reported in up to 4% of procedures in an early report,[32] which can be mitigated by lower CO_2 insufflation pressures as well as surgeon experience and continuous transesophageal echocardiographic monitoring.[33]

The large PREVENT IV trial (n = 3000) found that at 12 to 18 months, endoscopic harvesting was associated with higher SVG failure rates compared with open harvesting (46.7% vs 38.0%; $P < .001$).[34] At 3 years, all-cause mortality, myocardial infarction, and repeat revascularization were more frequent (20.2% vs 17.4%; adjusted hazard ratio, 1.22; 95% CI, 1.01-1.47; $P = .04$). In the EPIC trial (n = 183), endoscopic harvesting was associated with lower SVG patency at 9 months compared with open harvesting (79.2% vs 90.8%), which may be a result of variable endoscopic harvesting experience.[35] The recent Randomized Endo-Vein Graft Prospective (REGROUP) trial (n = 1150) found that the primary composite endpoint of all-cause mortality, nonfatal myocardial infarction, and repeat revascularization was similar following endoscopic and open harvesting at 2.8 years (13.9% vs 15.5%; $P = .47$) with experienced harvesters, although SVG patency specifically was not evaluated on imaging.[36] More recent intermediate findings of the REGROUP trial at a median follow-up of 4.7 years suggest a sustained comparable rate of MACE between endoscopic and open approaches.[37] Follow-up is planned for 10 years to assess long-term outcomes.

Although increasing evidence supports NT-SVG over skeletonized SVG with open techniques, endoscopic techniques have predominantly used skeletonized SVGs, and concerns remain regarding the quality of the SVGs and their longer-term patency. A recent, albeit small, case series highlighted the opportunity to have the best of both worlds by performing minimally invasive NT-SVG harvesting.[38] Given the predominance and wound advantages of endoscopic SVG harvesting, endoscopic rather than open NT-SVG harvesting seems more advantageous, but data related to this technique remain limited to date.[39]

SVG STORAGE SOLUTION

Grafts are traditionally stored in normal saline with added heparin or in autologous heparinized blood. However, normal saline is acidic and thus detrimental to vascular endothelium. Conversely, autologous heparinized blood has shown inconsistent findings across studies, with unclear benefits and harms.[40,41] Recently, balanced salt solutions with antioxidants and glutathione have been proposed as a better alternative to achieve a more physiologic pH, although the level of evidence remains minimal in the absence of larger trials (Table 1). An observational study conducted within the PREVENT IV trial suggested that vein grafts stored in buffered saline are associated with improved patency over time.[42] In an RCT (n = 125) comparing the intraoperative use of buffered solution with additional glutathione, L-ascorbic acid, and L-arginine (DuraGraft; Somahlution, Jupiter, Fla) versus heparinized saline, Perrault and associates[26] assessed wall thickness, lumen diameter, and maximum graft narrowing at 1, 3,

and 12 months and found comparable SVG wall thickness changes and graft occlusion at 3 months (primary outcome), whereas secondary graft outcomes at 12 months favored the test solution. Thus, further study is warranted to elucidate the effects of different storage solutions on intermediate and long-term SVG patency. In Europe, the prospective, multicentric VASC registry is assessing the safety and performance of treatment of vascular grafts with DuraGraft in 2964 CABG patients over 5 years (ClinicalTrials.gov identifier NCT02922088). The primary outcome assesses annual MACE rates up to 5 years; Secondary outcomes include MACCE rates at 1 month and annually up to 5 years, quality of life (via EQ-5D-5L) annually up to 5 years, and healthcare resource utilization costs annually up to 5 years.

PHARMACOTHERAPY

Secondary preventative therapies are essential to maintain graft patency. The AHA recommends the use of antiplatelet (class I; LoE A) and statin (class I; LoE A) therapy post-CABG for all patients.[43] Reduction of prothrombotic states post-CABG improves graft patency rates and prevents atherothrombotic complications. The AHA recommends that aspirin be administered preoperatively and within 6 hours post-CABG at doses of 81 to 325 mg daily and then continued indefinitely thereafter (class I; LoE A). The use of dual antiplatelet therapy over monotherapy with aspirin to improve graft patency is supported by the AHA in cases of off-pump CABG (class I; LoE A), but the benefits are not well established for patients with on-pump CABG (class IIb; LoE A). In a recent network meta-analysis (n = 4803),[44] high-certainty evidence that demonstrated the use of aspirin with clopidogrel (OR, 0.60; 95% CI, 0.42-0.86) or ticagrelor (OR, 0.50; 95% CI, 0.31-0.79) was associated with reduced graft occlusion compared with aspirin alone. However, when only studies with on-pump CABG were analyzed, the use of aspirin with ticagrelor (OR, 0.51; 95% CI, 0.32-0.80), but not with clopidogrel (OR, 0.68; 95% CI, 0.43-1.07) was associated with reduced graft vein occlusion. These results are encouraging, as dual antiplatelet therapy strategies do not appear to increase the risk of major bleeding or myocardial infarction in these patients. Nevertheless, trial evidence regarding single-antiplatelet (ticagrelor) versus dual antiplatelet (ticagrelor plus aspirin) therapy remains inconsistent. The Different Antiplatelet Therapy Strategy after CABG Surgery (DACAB) trial (n = 500)[45] showed improved 1-year SVG patency rates after elective CABG with ticagrelor plus aspirin versus aspirin alone (88.7% vs 76.5%; $P < .001$), whereas ticagrelor alone versus aspirin did not (82.8% vs 76.5%; $P = .10$). In DACAB, 75% of SVGs were performed with off-pump CABG,[46] which is consistent with meta-analytic findings suggesting a greater benefit from dual antiplatelet therapy in off-pump CABG patients.[47] The POPular CABG (Effect of Ticagrelor on

SVG Patency in Patients Undergoing CABG Surgery) trial, published after the network meta-analysis by Solo and associates,[44] randomized 499 patients to ticagrelor plus aspirin versus aspirin alone and found comparable SVG occlusion rates at 1 year (10.5% vs 9.1%; $P = .38$).[48] The ongoing Ticagrelor Antiplatelet Therapy to Reduce Graft Events and Thrombosis (TARGET) trial (ClinicalTrials.gov identifier NCT02053909) is randomizing 300 patients to 90 mg of ticagrelor twice daily versus 81 mg of aspirin twice daily to assess SVG occlusion and stenosis at 1 and 2 years.

SVG occlusion due to intimal hyperplasia and atheromatous plaques is related to increased levels of low-density lipoprotein (LDL). For this reason, the AHA recommends that all CABG patients receive statin therapy in the preoperative period and restart early after surgery (class I; LoE A). However, the intensity of therapy remains the subject of current debate. The target LDL of <100 mg/dL to prevent SVG disease was established in the Post-Coronary Artery Bypass Graft Trial[49] and supported by post hoc analysis of the Clopidogrel after Surgery for Coronary Artery Disease (CASCADE) trial.[50] Even though aggressive lowering of LDL to <70 mg/dL in patients with atherosclerotic disease improves cardiac outcomes, achieving this target in CABG patients might not be associated with improved graft patency, as a post hoc analysis of the CASCADE trial revealed no further improvement in graft patency for patients at an LDL of <70 mg/dL compared with <100 mg/dL. This is also supported by recent results from the Aggressive Cholesterol Therapy to Inhibit Vein Graft Events trial,[51] which revealed no difference in SVG occlusion at 1 year for patients who received 80 mg of atorvastatin compared with those who received 10 mg of atorvastatin. Currently, based on evidence from patients with clinical atherosclerotic cardiovascular disease, the AHA recommends high-intensity statin therapy for CABG patients age <75 years (class I; LoE A), owing to the potential for drug–drug interactions and lack of inclusion of patients age >75 years in the high-intensity statin trials. Finally, the multicentric NEWTON-CABG RCT (n = 766) is evaluating the effect of evolocumab on SVG patency, SVG disease rate, and complete SVG occlusion at 24 months after CABG (ClinicalTrials.gov identifier NCT03900026), in light of the higher PCSK9 levels observed in patients with SVG disease versus those with patent SVGs.[52]

In conclusion, conventional SVGs remain a popular choice of conduit but are subject to less favorable outcomes and patency compared with arterial grafts. However, various techniques exist to improve vein graft patency over time. Larger trials are nearing completion and will undoubtedly shed further light on the role of NT-SVG for non-LAD CABG. The 2021 update of the American College of Cardiology Foundation/AHA guidelines has been published recently, and multisociety guidelines for conduit selection are currently in development. Saphenous vein harvest site

complications are limited with endoscopic harvesting techniques and are safe in experienced hands. The results of the Food and Drug Administration's pivotal study of external stenting will be reported shortly. The use of balanced salt solutions and complementary pharmacotherapy may further enhance vein graft patency. Although the growing adoption and evidence in favor of multiple arterial grafting are promising, continuing improvements in SVG patency and outcomes for our patients remain essential.

Conflict of Interest Statement

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